

Original article

Intravascular Ultrasound Predictors of Major Adverse Cardiovascular Events After Implantation of Everolimus-eluting Stents for Long Coronary Lesions



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Article history:

Received 16 April 2016

Accepted 28 June 2016

Available online 25 October 2016

Keywords:

Coronary artery disease

Drug-eluting stent

Intravascular ultrasound

ABSTRACT

Introduction and objectives: There are limited data on the usefulness of intravascular ultrasound (IVUS) for long coronary lesions treated with second-generation drug-eluting stents. We evaluated IVUS predictors of major adverse cardiovascular events (MACE) 12 months after implantation of everolimus-eluting stents for long coronary lesions.

Methods: A total of 804 patients who underwent both postintervention IVUS examination and long everolimus-eluting stent (≥ 28 mm in length) implantation were included from 2 randomized trials. MACE was defined as a composite of cardiac death, myocardial infarction, and target-lesion revascularization.

Results: MACE occurred in 24 patients (3.0%) over 12 months. On multivariable Cox regression analysis, independent IVUS predictors of MACE included the postintervention minimum lumen area (MLA) at the target lesion (HR = 0.623; 95%CI, 0.433-0.895; $P = .010$) and the ratio of MLA/distal reference segment lumen area (HR = 0.744; 95%CI, 0.572-0.969; $P = .028$). The MLA and MLA-to-distal reference segment lumen area ratio that best predicted patients with MACE from those without these events were 5.0 mm² and 1.0, respectively. Patients with MLA < 5.0 mm² or a distal reference segment lumen area had a higher risk of MACE (HR = 6.231; 95%CI, 1.859-20.891; $P = .003$) than those without MACE.

Conclusions: Patients with a postintervention IVUS-measured MLA of < 5.0 mm² or a distal reference segment lumen area were at risk for MACE after long everolimus-eluting stent implantation.

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Predictores de eventos cardiovasculares adversos mayores en la ecocardiografía intravascular tras el implante de *stents* liberadores de everolimus en lesiones coronarias largas

RESUMEN

Introducción y objetivos: Hay poca información sobre la utilidad de la ecocardiografía intravascular (IVUS) en el tratamiento de lesiones coronarias largas con *stents* farmacoactivos de segunda generación. Se evaluaron por IVUS los predictores de eventos cardiovasculares adversos mayores (MACE) a los 12 meses del implante de *stents* liberadores de everolimus para el tratamiento de lesiones coronarias largas.

Métodos: Se incluyó a un total de 804 pacientes, procedentes de 2 ensayos clínicos aleatorizados, a los que se exploró por IVUS después del implante de un *stent* liberador de everolimus largo (≥ 28 mm). Los MACE se definieron como la combinación de eventos de muerte cardíaca, infarto de miocardio y revascularización de la lesión diana.

Resultados: Se produjeron MACE en 24 pacientes (3,0%) en 12 meses. En el análisis de regresión de Cox multivariable, los factores ecocardiográficos independientes predictivos fueron el área luminal mínima (ALM) de la lesión diana tras la intervención (HR = 0,623; IC95%, 0,433-0,895; $p = 0,010$) y el cociente ALM/área luminal del segmento de referencia distal (HR = 0,744; IC95%, 0,572-0,969; $p = 0,028$). Los valores del ALM y del cociente ALM/área luminal del segmento de referencia distal que predecían mejor qué pacientes sufrirían MACE diferenciándolos de los que no los tendrían fueron 5,0 mm² y 1,0

Palabras clave:

Enfermedad coronaria

Stent farmacoactivo

Ecocardiografía intravascular

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respectivamente. Los pacientes con ALM < 5,0 mm² o menor que el área luminal del segmento de referencia distal tenían mayor riesgo de MACE (HR = 6,231; IC95%, 1,859–20,891; p = 0,003).

Conclusiones: Los pacientes con un ALM medida con IVUS tras la intervención < 5,0 mm² o menor que el área luminal del segmento de referencia distal tuvieron más riesgo de MACE tras el implante de un *stent* liberador de everolimus largo.

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Abbreviations

DES: drug-eluting stent
 EES: everolimus-eluting stent
 IVUS: intravascular ultrasound
 MACE: major adverse cardiovascular events
 MLA: minimum lumen area
 TLR: target-lesion revascularization

INTRODUCTION

Contrary to bare metal stents, the clinical usefulness of intravascular ultrasound (IVUS) has not been clearly established with regard to percutaneous coronary intervention with drug-eluting stents (DES).^{1–8} Several meta-analyses have suggested that IVUS guidance may be associated with a lower risk of major adverse cardiovascular events (MACE) than angiographic guidance.^{2,4,6,7} However, randomized trials have failed to confirm the superiority of IVUS-guided DES implantation.^{1,3,5} Therefore, in the era of DES, the current guidelines recommend that IVUS may be considered in selected patients with complex lesions, such as left main coronary artery disease.^{9,10} Long-length DES implantation has increased the risk of in-stent restenosis compared with that occurring with shorter stents.^{11,12} Therefore, IVUS guidance may also be beneficial in patients with long coronary lesions. Recently, a randomized trial demonstrated that IVUS guidance for long DES implantation reduced target-lesion revascularization (TLR).¹³ Although previous IVUS studies showed that a threshold of stent expansion might predict in-stent restenosis after DES implantation,^{12,14} the data are still limited. This is especially true in patients with long coronary lesions. In addition, previous data were derived from retrospective observational studies or from the use of first-generation DES.^{12,14}

The aim of the present study was to identify IVUS predictors of MACE in a large series of patients treated with long-length everolimus-eluting stents (EES) from prospective randomized trials. This type of stent is one of the most widely used second-generation DES in current clinical practice.¹⁵

METHODS

Study Population

Patients were identified from 2 randomized trials: the RESET trial¹⁶ and the IVUS-XPL trial.¹³ Briefly, the RESET trial was a randomized, noninferiority trial that compared 3-months of dual antiplatelet therapy following implantation of the Endeavor sprint zotarolimus-eluting stents (Medtronic, Inc.; Santa Rosa, California,

United States) with 12 months of dual antiplatelet therapy following implantation of another DES. In the prespecified long lesion subset of this study,^{5,16} 543 patients were randomly allocated to receive either the Endeavor sprint zotarolimus-eluting stent or the EES (Xience V, Abbott Vascular; Santa Clara, California, United States). The patients were then randomly assigned to either IVUS- or angiography-guided DES implantation (2 × 2 design). In the other randomized IVUS-XPL trial, which implanted EES (Xience prime, Abbott Vascular) in patients with long coronary lesions, 1400 patients were randomly assigned to receive either IVUS- or angiography-guided EES implantation. Detailed protocols of these trials have previously been described.^{5,13,16} A total of 804 patients from these 2 trials who underwent both postintervention IVUS examination and long EES (≥ 28 mm in length) implantation were finally included in this study, with 127 patients from the RESET trial and 677 patients from the IVUS-XPL trial. The study protocols of these trials were approved by the institutional review board of each participating institution, and written consent was obtained from all patients.

Percutaneous Coronary Intervention and Pharmacological Therapy

Everolimus-eluting stent implantation was performed according to standard techniques. Overlapping stents were used if a lesion could not be covered with a single stent. The stent diameter and length were selected using online IVUS measurements. Adjunct high-pressure dilation was performed at the operators' discretion, based on the IVUS findings.^{5,13} Use of IVUS was allowed at any step of EES implantation (before, during, or after implantation). The IVUS examinations before and during EES implantation were not mandatory; however, postintervention IVUS examination was mandatory.^{5,13} In the IVUS-XPL trial, the postintervention IVUS criteria for stent optimization were defined as a minimal lumen cross-sectional area greater than the lumen cross-sectional area at the distal reference segments.¹³ One of 2 commercially available IVUS systems was used (Atlantis or I-Lab, Boston Scientific Corp./SCIMED; Minneapolis, Minnesota, United States, or Eagle Eye, Volcano Therapeutics; Rancho Cordova, California, United States).

At least 12 hours prior to EES implantation, all patients received loading doses of aspirin (100 mg) and clopidogrel (300 mg). However, if this loading dose of clopidogrel was not administered, the patient instead received a 600-mg loading dose in the catheterization laboratory immediately prior to percutaneous coronary intervention. Unfractionated heparin was administered intraoperatively to maintain an activated clotting time longer than 250 seconds. Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. After EES implantation, aspirin (100 mg, daily) was prescribed indefinitely. The duration of clopidogrel administration (75 mg, daily) depended on the randomized assignments of the RESET and IVUS-XPL trials. Notably, all patients

from the RESET trial were allocated to 12 months of dual antiplatelet therapy.

Angiographic and Intravascular Ultrasound Analysis

Angiographic and IVUS measurements were performed by analysts who were blinded to patient and treatment assignments in an independent core laboratory at the Cardiovascular Research Center, Seoul, Korea. Before and after EES implantation, an off-line quantitative coronary angiographic system (CASS system, Pie Medical Instruments; Maastricht, The Netherlands) was used to perform quantitative coronary angiography analysis. Using the guiding catheter for magnification-calibration, the diameters of the reference vessel (the average of the proximal and distal reference lumen diameters) and the minimal luminal diameter were measured before and after EES implantation. These measurements were made from diastolic frames in a single matched view, revealing the smallest minimal luminal diameter.

Standardized planimetry of the lumen, stent, and vessel cross-sectional area was performed using planimetry software (Echo-plaque, INDEC Systems; Santa Clara, California, United States) in accordance with IVUS guidelines from the American College of Cardiology.¹⁷ The target lesion and both proximal and distal reference segments were assessed quantitatively. The postintervention target lesion site was the image slice with the minimum lumen area (MLA). The proximal and distal reference segments were the most normal-looking segments within 5 mm proximal and distal to the target lesion, respectively.

Follow-up and Study Endpoints

After EES implantation, clinical assessments were performed in the hospital and at 1, 3, 6, and 12 months after discharge. The follow-up assessments were performed during a clinic visit or by telephone interview. MACE was defined as a composite of cardiac death, target lesion-related myocardial infarction, and ischemia-driven TLR.

Clinical events were defined according to the Academic Research Consortium and the expert consensus document of the third universal definition of myocardial infarction.^{18,19} All deaths were considered cardiac unless an unequivocal noncardiac cause could be established.¹⁸ At the 1-year follow-up, a target lesion-related myocardial infarction was defined by the following parameters: the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of myocardial infarction, and an increase in the creatine kinase myocardial band fraction above the upper normal limits or an increase in troponin-T/troponin-I above the 99th percentile of the upper limit of normal. The territory of the myocardial infarction was supplied by the coronary artery containing the stented lesions (implanted stent \geq 28 mm in length).^{13,19} Ischemia-driven TLR was defined as a repeat percutaneous coronary intervention or bypass surgery of the target lesion with either of the following: a) angiographic diameter stenosis \geq 50% by quantitative coronary angiographic analysis with documentation of a positive stress test, or b) angiographic diameter stenosis \geq 70% irrespective of the stress test results.¹⁸

Statistical Analysis

Statistical analysis was performed using SPSS (version 18.0.0, SPSS Inc.; Chicago, Illinois, United States). Categorical variables are reported as numbers and percentages and were compared using the chi-square test or Fisher's exact test. In contrast,

continuous variables are reported as mean \pm standard deviation or median [interquartile range] and were compared using the Student *t* test or Mann-Whitney *U* test (if data were skewed). Multivariable Cox regression analysis was performed to determine the independent IVUS predictors of MACE during the 12 months of follow-up. Variables from univariate analysis with *P* values $<$.1 were included in the multivariable model. Receiver operator characteristic analysis was performed to determine the best cutoff values for the independent IVUS predictors of MACE. Simple linear regression analysis was also performed to evaluate the association between the size of the reference vessel and IVUS findings. All *P* values were 2-sided. A *P* value $<$.05 was considered statistically significant.

RESULTS

A total of 24 (3%) of the 804 patients who underwent EES implantation experienced MACE during the 12 months of follow-up. Three patients died, 3 had target lesion-related myocardial infarctions, and 22 experienced ischemia-driven TLR. Of these, 2 patients died of myocardial infarction without revascularization treatment, and another patient died after a myocardial infarction, despite emergent revascularization.

The clinical characteristics at the index procedure are listed in [Table 1](#). There were no significant differences in clinical characteristics between patients with and without MACE. The lesional and procedural characteristics in the 2 groups are shown in [Table 2](#). After EES implantation, as compared with the 780 patients without MACE, the 24 patients with MACE had a smaller minimum lumen diameter (2.4 ± 0.4 mm vs 2.6 ± 0.4 mm; *P* = .019) and larger-diameter stenoses ($17.9\% \pm 7.3\%$ vs $12.7\% \pm 8.5\%$; *P* = .005) on quantitative coronary angiographic analysis. In the postintervention IVUS analysis, the 24 patients with MACE showed smaller MLA (4.4 ± 1.1 mm² vs 5.8 ± 1.8 mm²; *P* $<$.001), lower ratios of MLA to distal reference segment lumen area (0.9 ± 0.2 vs 1.0 ± 0.2 ; *P* $<$.001), and lower ratios of MLA to average reference segment lumen area (0.7 ± 0.2 vs 0.8 ± 0.2 ; *P* = .001) compared with the patients without MACE.

The IVUS predictors of MACE are shown in [Table 3](#). On multivariable Cox regression analysis, the independent predictors of MACE included postintervention MLA (hazard ratio [HR] = 0.623; 95% confidence interval [95%CI], 0.433–0.895; *P* = .010) and the ratio of MLA to distal reference segment lumen area (HR = 0.744; 95%CI, 0.572–0.969; *P* = .028). The area under the curve on the receiver operator characteristics curve of the MLA, the ratio of MLA to distal reference segment lumen area, and the combination model of MLA and the ratio of MLA-to-distal reference segment lumen area was 0.731 (95%CI, 0.652–0.811; *P* $<$.001), 0.696 (95%CI, 0.585–0.807; *P* = .001), and 0.766 (95%CI, 0.691–0.841; *P* $<$.001), respectively.

Sensitivity and specificity curves were used to identify the optimal cutoff values of MLA and the ratio of MLA-to-distal reference segment lumen area that best predicted MACE after EES implantation ([Figure 1](#)): 5.0 mm² for MLA and 1.0 for the ratio of MLA to distal reference segment lumen area. The sensitivity and specificity for MLA $<$ 5.0 mm² were 66.7% (16 of 24) and 64.6% (504 of 780), respectively. The positive and negative predictive values were 5.5% (16 of 292) and 98.4% (504 of 512), respectively. The sensitivity and specificity for MLA smaller than the distal reference segment lumen area to predict MACE were 62.5% (15 of 24) and 62.1% (484 of 780), respectively. The positive and negative predictive values were 4.8% (15 of 311) and 98.2% (484 of 493), respectively.

Twenty-one (87.5%) of the 24 patients with MACE had a postintervention MLA $<$ 5.0 mm² or smaller than the distal

Table 1
Baseline Clinical Characteristics

	MACE (n = 24)	Non-MACE (n = 780)	P
Age, y	65.3 ± 9.2	63.2 ± 9.2	.276
Male sex	16 (66.7)	538 (69.0)	.810
Hypertension	16 (66.7)	504 (64.6)	.836
Diabetes mellitus	10 (41.7)	269 (34.5)	.467
Dyslipidemia	17 (70.8)	526 (67.4)	.726
Current smoker	7 (29.2)	163 (20.9)	.328
Prior myocardial infarction	0 (0.0)	33 (4.2)	.619
Acute myocardial infarction	5 (20.8)	102 (13.1)	.353
Multivessel disease	15 (62.5)	519 (66.5)	.680
Multivessel stent implantation	7 (29.2)	233 (29.9)	.941
Duration of dual antiplatelet therapy (mo)	12.0 [6.0-12.0]	12.0 [6.0-12.0]	.835

MACE, major adverse cardiovascular events.

Data are presented as No. (%), mean ± standard deviation, or median [interquartile range].

reference segment lumen area. The MACE rate was 0.8% (3 of 372) in patients who had neither MLA < 5.0 mm² nor smaller than the distal reference segment lumen area, and was 4.9% (21 of 432) in patients who had at least 1 of these variables (HR = 6.231; 95%CI,

1.859-20.891; P = .003). (Figure 2, Table of the supplementary material).

The absolute value of MLA measured by postintervention IVUS analysis was significantly associated with the diameter of the

Table 2
Lesional and Procedural Characteristics

	MACE (n = 24)	Non-MACE (n = 780)	P
Coronary arteries			.952
Left anterior descending artery	17 (70.8)	504 (64.6)	
Left circumflex artery	3 (12.5)	112 (14.4)	
Right coronary artery	4 (16.7)	164 (21.0)	
Quantitative coronary angiography analysis			
<i>Preintervention</i>			
Reference vessel diameter, mm	2.8 ± 0.4	2.9 ± 0.5	.450
Minimum lumen diameter, mm	0.9 ± 0.3	0.9 ± 0.4	.688
Diameter stenosis, %	68.9 ± 9.6	70.5 ± 14.4	.450
Lesion length (mm)	37.0 ± 8.9	34.7 ± 11.3	.341
<i>Postintervention</i>			
Reference vessel diameter, mm	3.0 ± 0.4	3.0 ± 0.4	.545
Minimum lumen diameter, mm	2.4 ± 0.4	2.6 ± 0.4	.019
Diameter stenosis, %	17.9 ± 7.3	12.7 ± 8.5	.005
Stent overlap	9 (37.5)	232 (29.7)	.414
Stent diameter, mm	3.0 ± 0.3	3.1 ± 0.4	.121
Stent length, mm	42.7 ± 16.1	39.7 ± 13.4	.286
Adjunct postdilation	17 (70.8)	566 (72.6)	.852
Final balloon size, mm	3.1 ± 0.4	3.1 ± 0.4	.616
Maximal inflation pressure, atm	16.7 ± 2.2	16.5 ± 4.0	.762
Postintervention IVUS analysis			
Proximal reference segment EEM area, mm ²	16.2 ± 4.8	17.3 ± 5.1	.345
Proximal reference segment lumen area, mm ²	8.1 ± 3.1	8.9 ± 3.3	.198
Proximal reference segment plaque area, mm ²	8.1 ± 3.2	8.4 ± 3.7	.372
Proximal reference segment plaque burden, %	50.0 ± 12.2	47.9 ± 12.8	.252
MLA, mm ²	4.4 ± 1.1	5.8 ± 1.8	<.001
Distal reference segment EEM area, mm ²	9.4 ± 4.2	10.1 ± 3.9	.436
Distal reference segment lumen area, mm ²	5.4 ± 1.6	5.8 ± 1.7	.244
Distal reference segment plaque area, mm ²	3.9 ± 3.6	4.3 ± 2.8	.455
Distal reference segment plaque burden, %	41.2 ± 15.3	39.0 ± 13.7	.390
MLA-to-distal reference segment lumen area ratio	0.9 ± 0.2	1.0 ± 0.2	<.001
MLA-to-average reference segment lumen area ratio	0.7 ± 0.2	0.8 ± 0.2	.001

EEM, external elastic membrane; IVUS, intravascular ultrasound; MACE, major adverse cardiovascular events; MLA, minimum lumen area. Data are presented as No. (%) or mean ± standard deviation.

Table 3
Intravascular Ultrasound Predictors of Major Adverse Cardiac Events at 12 Months of Follow-up

Postpercutaneous coronary intervention	Univariate analysis		Multivariable analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
MLA, per 1.0 mm ²	0.520 (0.373-0.723)	< .001	0.623 (0.433-0.895)	.010
MLA-to-distal reference lumen area ratio, per 0.1	0.626 (0.503-0.780)	< .001	0.744 (0.572-0.969)	.028
MLA-to-average reference lumen area ratio, per 0.1	0.655 (0.508-0.845)	.001	0.975 (0.696-1.364)	.881

95%CI, 95% confidence interval; HR, hazard ratio; MLA, minimum lumen area.

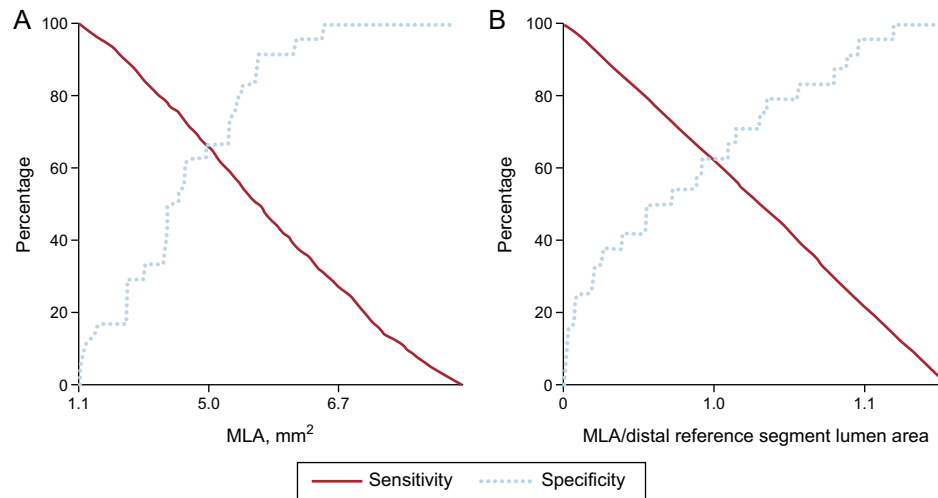


Figure 1. Sensitivity and specificity curves to identify the optimal thresholds of MLA and the ratio of MLA-to-distal reference segment lumen area. The optimal thresholds were 5.0 mm² (A) and 1.0 (B). MLA, minimum lumen area.

distal reference vessel measured by preintervention quantitative coronary angiographic analysis (coefficient = 2.168; 95%CI, 1.965-2.370; $P < .001$). In contrast, the ratio of MLA to distal reference segment lumen area was not (Figure 3). In the subset of 320 patients with a distal reference vessel diameter < 2.5 mm, there was a lower incidence of MACE in patients with an MLA equal to or greater than the distal reference segment lumen area (1.6%, 3 of 193 patients) (HR = 0.215; 95%CI, 0.058-0.795; $P = .021$) compared with that in patients with an MLA smaller than distal reference segment lumen area (7.1%, 9 of 127 patients).

DISCUSSION

In this pooled analysis of 804 patients treated with IVUS-guided long EES implantation, the overall MACE rate was 3% at 12 months. Two independent IVUS predictors of MACE were an absolute MLA value of 5.0 mm² and a relative enlargement of the MLA to the distal reference segment lumen area. In particular, these 2 predictors showed high negative predictive values.

The MACE rate in this study was lower than that of the COMPARE trial, in which a composite of cardiac death, nonfatal

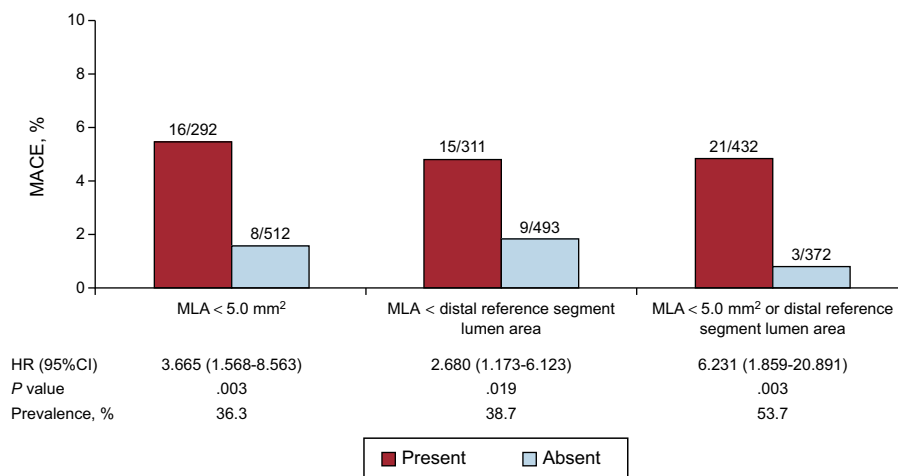


Figure 2. Major adverse cardiovascular events rate for patients with and without MLA < 5.0 mm² or distal reference segment lumen area, at 12 months of follow-up. Patients with MLA < 5.0 mm² or distal reference segment lumen area had an increased risk of MACE (HR = 6.231; 95%CI, 1.859-20.891; $P = .003$). 95%CI, 95% confidence interval; HR, hazard ratio; MACE, major adverse cardiovascular events; MLA, minimum lumen area.

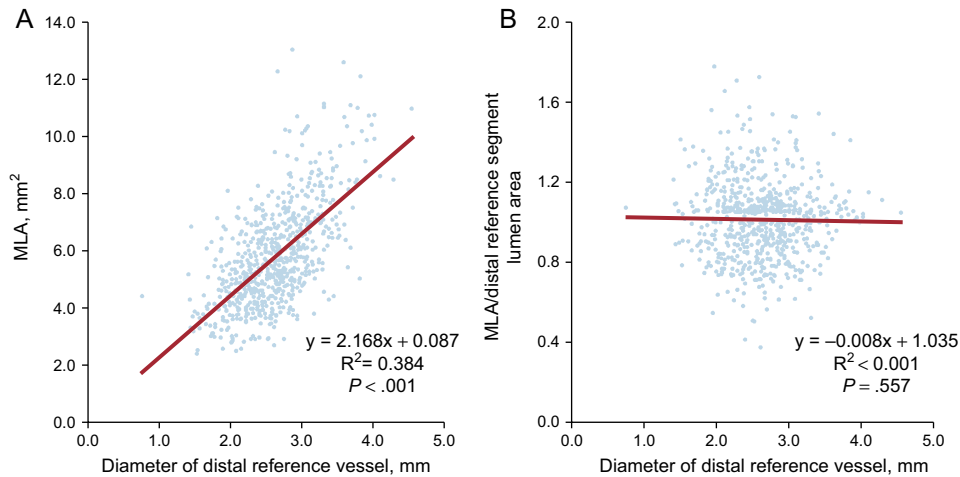


Figure 3. Association between the diameter of distal reference vessel on preintervention angiography and MLA measured by postintervention intravascular ultrasound. The size of the distal reference vessel was associated with postintervention MLA (A), but not with the ratio of MLA-to-distal reference segment lumen area (B). MLA, minimum lumen area.

myocardial infarctions, and clinically justified TLR occurred in 5% of 897 patients after 12 months.²⁰ Compared with the COMPARE trial (54%), postdilatation was more frequently performed in the present study (72%), which might have resulted from IVUS guidance. Consequently, the postintervention minimum lumen diameter (2.6 mm) of the present study was larger than that (2.1 mm) of the COMPARE trial.²⁰ Among excluded patients from the present study due to angiography guidance, the MACE rate was 7% in the RESET trial and 6% in the IVUS-XPL trial, respectively. These findings were consistent with the COMPARE trial.²⁰

A previous IVUS study showed that the relative parameter (ie, ratio of MLA to reference segment lumen cross-sectional area) was significantly associated with in-stent restenosis after bare metal stent implantation.²¹ However, in the DES era, the absolute parameter (ie, MLA) has been considered to be more predictive for adequate stent patency or angiographic restenosis than the relative parameter.^{12,14,22} In the IVUS substudy of the SIRIUS trial with 72 patients,²² the optimal threshold of postintervention MLA to predict an 8-month follow-up MLA $> 4 \text{ mm}^2$ was 5.0 mm^2 for the sirolimus-eluting stent. The sensitivity, specificity, and positive predictive value with this cutoff value were 76%, 83%, and 90%, respectively. A previous angiographic follow-up study (550 patients, 670 native coronary lesions) based on real-world registry data similarly showed that an MLA of 5.5 mm^2 was associated with angiographic restenosis at the 6-month follow-up. However, the sensitivity, specificity, and positive predictive value were relatively low (67%, 67%, and 7%, respectively) compared with those of the SIRIUS trial substudy.¹² Similarly, a recent registry study with 229 EES-treated patients suggested that the optimal postintervention MLA was 5.4 mm^2 to predict 9-month follow-up angiographic restenosis¹⁴ (which was consistent with the present finding of MLA of 5.0 mm^2). Contrary to previous studies,^{12,14,22} this study was derived from 2 large prospective, randomized (IVUS- vs angiography-guided) trials. Both of these trials employed second-generation DES (ie, EES).

There are limited data on the clinical usefulness of relative IVUS parameters for DES optimization. One study, which applied the IVUS criteria of DES optimization of $\text{MLA} \geq 5 \text{ mm}^2$ or $> 90\%$ of distal reference segment lumen area for small vessel, failed to demonstrate the superiority of IVUS guidance ($n = 105$ patients) over angiography guidance ($n = 105$ patients). However, this trial was extremely underpowered, and did not include analysis of IVUS optimization.¹ A recent, randomized IVUS-XPL trial reported the

clinical usefulness of relative IVUS parameters for stent optimization, which included MLA greater than distal reference segment lumen area in IVUS-guided long EES-treated patients. The patients in that trial ($n = 315$) who did not meet the IVUS criteria had a significantly higher incidence of the primary endpoint compared with those ($n = 363$) meeting the criteria for stent optimization (4.6% vs 1.5%; $P = .017$, respectively).¹³ In this pooled analysis, there was a significant association with MACE occurrence and patients with an MLA less than the distal reference segment lumen area, even after adjustment of the absolute parameter. Even in the DES era, achieving adequate stent dimensions is still important in order to minimize restenosis and stent thrombosis. If not, stent underexpansion may cause abnormal shear stress that potentially affects neointimal hyperplasia or thrombosis formation. In long lesions, the atherosclerotic disease is diffusely distributed. Therefore, the distance from segments with the smallest lumen diameter to the distal reference segment is quite long. In addition, there is a greater difference in the reference vessel size (larger proximal reference vessel size vs smaller distal reference vessel size) in diffuse long lesions compared with that of shorter lesions.²³ When longer stent implantation is considered in the treatment of diffuse long lesions, the distal margin of a long stent is frequently placed adjacent to the distal reference segment with small vessel size. This situation inevitably creates a practical dilemma. Achieving an $\text{MLA} \geq 5 \text{ mm}^2$ is mechanically impossible in the distal part of the stented segment adjacent to the small-sized distal reference segment. In this study, postintervention MLA was limited by a preintervention distal reference segment diameter (Figure 3). Therefore, another IVUS criterion of stent optimization is required when the distal margin of the stented segment is placed adjacent to a small-sized distal reference segment. In the present study, 320 (39.8%) of 804 EES-treated patients had a distal reference vessel diameter of $< 2.5 \text{ mm}$. In these subgroup patients, the achievement of $\text{MLA} \geq$ distal reference segment lumen area was significantly associated with a lower incidence of MACE compared with patients with an MLA smaller than the distal reference segment lumen area.

Study Limitations

The 2 trials had different study designs, and the patients included from these randomized trials might not reflect real-world

clinical practice. Since the preintervention IVUS information was not available in the current dataset of this study, the impact of preintervention IVUS on MACE could not be assessed. Accordingly, the interpretations should be limited within the present findings. The associations between detailed interventional procedures and postintervention IVUS findings could not be evaluated because the analyzed IVUS data were drawn from final reports written after the completion of the intervention. Long lesions of the right coronary artery were relatively rare in patients with MACE. The cost-effectiveness of IVUS evaluation was beyond the scope of this study. Finally, in practice, the achievement of these suggested IVUS criteria may be not always feasible because lesion characteristics such as heavy calcification also inhibit adequate lumen enlargement. In the present study, the frequency of patients with MLA < 5.0 mm² or distal reference segment lumen area was 53.7% (432 of 804), as shown in Figure 2. The present study did not evaluate the impacts of preintervention IVUS or the IVUS findings from subsequent actions (such as adjuvant dilatation with a larger balloon) taken after IVUS examination during DES implantation. Accordingly, further investigations are required to elucidate the clinical impacts of the suggested IVUS criteria.

CONCLUSIONS

This pooled analysis of 804 patients demonstrated that the overall MACE rate was 3% during the first 12 months after IVUS-guided long EES implantation. Independent predictors of MACE were MLA and the ratio of the MLA-to-distal reference segment lumen area, as assessed by postintervention IVUS. The optimal MLA cutoff values and the ratio of MLA-to-distal reference segment lumen area that predicted MACE were 5.0 mm² and 1.0, respectively. Therefore, there is a risk of MACE in patients with a postintervention MLA < 5.0 mm² or a distal reference segment lumen area after long EES implantation.

WHAT IS KNOWN ABOUT THE TOPIC?

- Although previous IVUS studies showed that a threshold of stent expansion might predict in-stent restenosis after DES implantation, the data are still limited. This is especially true in patients with long coronary lesions. In addition, previous data were derived from retrospective observational studies or from the use of first-generation DES.

WHAT DOES THIS STUDY ADD?

- Patients with a postintervention IVUS-measured MLA of less than 5.0 mm² or a distal reference segment lumen area were at risk for MACE after long EES implantation.

FUNDING

This study was supported by a grant from the Korea Healthcare Technology Research and Development Project, Ministry for Health and Welfare, Republic of Korea (Nos. A085136 and HI15C1277), the Mid-career Researcher Program through a National Research Foundation of Korea grant funded by the Ministry of Education, Science and Technology, Republic of Korea (No. 2015R1A2A2A01002731), and the Cardiovascular Research Center, Seoul, Korea.

CONFLICTS OF INTEREST

None declared.

SUPPLEMENTARY MATERIAL



Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2016.06.019.

REFERENCES

1. Jakabcin J, Spacek R, Bystron M, et al. Long-term health outcome and mortality evaluation after invasive coronary treatment using drug eluting stents with or without the IVUS guidance. Randomized control trial. HOME DES IVUS. *Catheter Cardiovasc Interv.* 2010;75:578–583.
2. Zhang Y, Farooq V, Garcia-Garcia HM, et al. Comparison of intravascular ultrasound versus angiography-guided drug-eluting stent implantation: a meta-analysis of one randomized trial and ten observational studies involving 19,619 patients. *EuroIntervention.* 2012;8:855–865.
3. Chieffo A, Latib A, Caussin C, et al. A prospective, randomized trial of intravascular-ultrasound guided compared to angiography guided stent implantation in complex coronary lesions: the AVIO trial. *Am Heart J.* 2013;165:65–72.
4. Klersy C, Ferlini M, Raisaro A, et al. Use of IVUS guided coronary stenting with drug eluting stent. *Int J Cardiol.* 2013;170:54–63.
5. Kim JS, Kang TS, Mintz GS, et al. Randomized comparison of clinical outcomes between intravascular ultrasound and angiography-guided drug-eluting stent implantation for long coronary artery stenoses. *J Am Coll Cardiol Interv.* 2013; 6:369–376.
6. Jang JS, Song YJ, Kang W, et al. Intravascular ultrasound-guided implantation of drug-eluting stents to improve outcome: a meta-analysis. *J Am Coll Cardiol Interv.* 2014;7:233–243.
7. Ahn JM, Kang SJ, Yoon SH, et al. Meta-analysis of outcomes after intravascular ultrasound-guided versus angiography-guided drug-eluting stent implantation in 26,503 patients enrolled in three randomized trials and 14 observational studies. *Am J Cardiol.* 2014;113:1338–1347.
8. Witzensbichler B, Maehara A, Weisz G, et al. Relationship between intravascular ultrasound guidance and clinical outcomes after drug-eluting stents: the Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study. *Circulation.* 2014;129:463–470.
9. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol.* 2011;58:e44–e122.
10. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the task force on myocardial revascularization of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. *Eur Heart J.* 2014;35:2541–2619.
11. Lemos PA, Hoyer A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation.* 2004;109: 1366–1370.
12. Hong MK, Mintz GS, Lee CW, et al. Intravascular ultrasound predictors of angiographic restenosis after sirolimus-eluting stent implantation. *Eur Heart J.* 2006;27:1305–1310.
13. Hong SJ, Kim BK, Shin DH, et al. Effect of intravascular ultrasound-guided vs angiography-guided everolimus-eluting stent implantation: the IVUS-XPL Randomized Clinical Trial. *JAMA.* 2015;314:2155–2163.
14. Song HG, Kang SJ, Ahn JM, et al. Intravascular ultrasound assessment of optimal stent area to prevent in-stent restenosis after zotarolimus-, everolimus-, and sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv.* 2014;83: 873–878.
15. Choi YJ, Kim JB, Cho SJ, et al. Changes in the Practice of Coronary Revascularization between 2006 and 2010 in the Republic of Korea. *Yonsei Med J.* 2015;56:895–903.
16. Kim BK, Hong MK, Shin DH, et al. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol.* 2012;60:1340–1348.
17. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies. A report of the American College of Cardiology task force on clinical expert consensus documents. *J Am Coll Cardiol.* 2001;37:1478–1492.
18. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344–2351.
19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012;60:1581–1598.

20. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet*. 2010;375:201–209.
21. Moussa I, Moses J, Di Mario C, et al. Does the specific intravascular ultrasound criterion used to optimize stent expansion have an impact on the probability of stent restenosis? *Am J Cardiol*. 1999;83:1012–1017.
22. Sonoda S, Morino Y, Ako J, et al. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the SIRIUS trial. *J Am Coll Cardiol*. 2004;43:1959–1963.
23. Cho S, Shin DH, Kim JS, et al. Rationale and design: impact of intravascular ultrasound guidance on long-term clinical outcomes of everolimus-eluting stents in long coronary lesions. *Contemp Clin Trials*. 2015;40:90–94.